SPATIOTEMPORAL DYNAMICS OF PACING IN MODELS OF ANATOMICAL REENTRY

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Abstract-**Reentry around non-conducting ventricular scar tissue, which often causes lethal arrhythmias, is typically treated by rapid stimulation from an implantable defibrillator. However, the mechanisms of termination (success and failure) are poorly understood. To elucidate such mechanisms, we studied pacing of anatomical reentry in 1-D and 2-D excitable cardiac media models. Our results suggest that the existence of inhomogeneity in the reentry circuit is essential for pacing termination of tachycardia to be successful. Considering the role of such inhomogeneities may lead to more effective pacing algorithms.**

Keywords **- Reentry, tachycardia, antitachycardia pacing**

I. INTRODUCTION

Trains of local electrical impulses are widely used to restore normal wave propagation in the heart during tachycardia - but this process is not always successful. Such "antitachycardia pacing" may inadvertently induce tachycardias or cause tolerated tachycardias to degenerate to more rapid and threatening tachyarrhythmias. It is known from clinical electrophysiology studies that pacing to terminate uniform ventricular tachycardia (VT) can cause tachycardia acceleration or degeneration to ventricular fibrillation (VF) [1]. The underlying mechanisms governing the success or failure of a pacing algorithm are not yet clear. Understanding these mechanisms is essential, as a better knowledge of the processes involved in the suppression of VT through ventricular extrastimuli pacing can aid in the design of more effective therapies. The reentrant action potential may propagate around an inexcitable obstacle ("anatomical reentry") or may reside in a region of the myocardium that is excitable in its entirety ("functional reentry") [2]. Although studies on the role of pacing in eliminating tachycardia have been done for functional reentry [3], there has been little work done for the case of anatomical reentry [4].

Several factors influence the ability of extrastimuli and/or rapid pacing to interact with VT. The most prominent are [5]: (a) VT cycle length (for anatomical reentry this is determined by the length of the VT circuit around the obstacle), (b) the refractory period at the stimulation/pacing site and in the VT circuit, (c) the conduction time from the pacing site to the VT circuit, and (d) the duration of the excitable gap. As there are a number of conditions to be satisfied before reentry is successfully terminated, a single extrastimulus is rarely sufficient. Multiple stimuli are often used - where the first extrastimulus is believed to "peel back" refractoriness to allow the subsequent extrastimuli to interact with the circuit more prematurely than was possible with only a single extrastimulus.

There has been substantial work on computer modeling of pacing termination of tachyarrhythmias in a one-dimensional ring [2, 6]. The termination of reentry in such a geometry (which is effectively that of the reentry circuit immediately surrounding an anatomical obstacle) occurs in the following manner. Each extrastimulus splits into two branches while traveling around the reentry circuit. The retrograde branch (proceeding opposite to the direction of the reentrant wave) ultimately collides with the reentrant excitation, causing mutual annihilation. The anterograde branch (proceeding along the direction of the reentrant wave) can, depending on the timing of the stimulation, lead to either resetting, where the anterograde wave becomes the new reentrant wave, or termination of reentry, where the anterograde wave gets blocked by the refractory end of the original reentrant wave. From continuity arguments, it can be shown that there exists a range of extrastimuli phases and amplitudes that leads to successful reentry termination [6]. Unfortunately, the argument is essentially applicable only to a 1D model - the process is crucially dependent on the fact that the pacing site is on the reentry circuit itself. In reality, however, it is unlikely that the pacing site will be so fortuitously located.

In this study, we examine the dynamics of pacing from a site some distance away from the reentry circuit. One then has to consider the passage of the extrastimulus from the pacing site to the reentry circuit. Because the reentrant circuit is the origin of rapid outwardly propagating waves, the extrastimulus will be annihilated before it reaches the circuit under most circumstances. Successful propagation to the reentry circuit will require utilising multiple extrastimuli to "peel back" refractory tissue incrementally until one successfully arrives at the circuit. Further, the anterograde branch must be blocked by the refractory tail of the reentrant wave. However, as outlined in detail in the Discussion section of our paper, this is extremely unlikely to happen in a homogeneous medium. As shown by our simulation results, the existence of inhomogeneity in the reentry circuit seems essential for pacing termination of VT.

II. METHODOLOGY

Modified Fitzhugh-Nagumo type excitable media model equations of ventricular activation were used to simulate the interaction of extrastimuli with the VT circuit around an anatomical obstacle. For the 1D model we used the Panfilov model [7, 8] defined by the two equations governing the excitability e and recovery g variables:

$$\begin{aligned} \partial e/\partial t &= \nabla^2 e - f(e) - g, \\ \partial g/\partial t &= \epsilon(e,g)(ke - g). \end{aligned} \tag{1}$$

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Abstract

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The function $f(e)$, which specifies fast processes (e.g., the initiation of the action potential) is piecewise linear: $f(e) = C_1 e$, for $e < e_1$, $f(e) = -C_2 e + a$, for $e_1 \leq e \leq e_2$, and $f(e) = C_3(e-1)$, for $e > e_2$. The function $\epsilon(e,g)$, which determines the dynamics of the recovery variable, is $\epsilon(e,g) = \epsilon_1$ for $e < e_2$, $\epsilon(e,g) = \epsilon_2$ for $e > e_2$, and $\epsilon(e,g) = \epsilon_3$ for $e < e_1$ and $g < g_1$. We use the physically appropriate parameter values given in Ref. [9]. For the 2D studies, in addition to the Panfilov model we used two other two-variable modified Fitzhugh-Nagumo type models: the Aliev-Panfilov model [10], which simulates the restitution property of cardiac tissue, as well as the model proposed by Kogan *et al* [11], which simulates the restitution and dispersion properties of cardiac tissue.

We solve the models by using a forward-Euler integration scheme. We discretise our system on a grid of points in space with spacing $\delta x = 0.5$ dimensionless units and use the standard three- and five-point difference stencils for the Laplacians in spatial dimensions $d = 1$ and 2 respectively. Our spatial grid consists of a linear lattice with L' points or a square lattice with $L \times L$ points; in our studies we have used values of L' ranging from 500 to 1000 and $128 \leq L \leq 256$. Our time step is $\delta t = 0.022$ dimensionless units. We define dimensioned time T to be 5 ms and 1 spatial unit to be 1 mm.

Our initial condition is a wave front at some point in the medium with transient conduction block on one side to permit wavefront propagation along a single direction only. The conduction block is realised by making the corresponding region refractory. This initiates a re-entrant wave which roughly corresponds to an anatomically-mediated tachycardia. Extrastimuli are then introduced from a pacing site. In the 1D model, the ends have periodic boundary conditions - such that the medium represents a ring of cardiac tissue around an inexcitable obstacle. In the 2D models, for top and bottom ends we use no-flux (Neumann) boundary conditions since the ventricles are electrically insulated from the atria (top) and the waves converge and annihilate at the region around the apex (bottom). For the sides, we use periodic boundary conditions. Two square patches of inexcitable region (whose conductivity constant is zero) are placed about the centre of the simulation domain with a narrow passage for wave propagation between them (Fig. 1). No-flux boundary conditions are used at the interface between the active medium and the inexcitable obstacle. We use this arrangement to represent anatomical obstacles (e.g., scar tissue) around which "figure-of-eight" reentry can occur. This kind of pattern has been seen previously in actual cardiac tissue (e.g., in post healed myocardial infarction tissue [12]).

III. RESULTS

In the 2D simulations we looked at the effectiveness of different pacing algorithms in terminating figure-of-eight reentry. The pacing was simulated by a planar wave initiated at the base of the simulation domain. This represents a wave that has propagated a fixed distance up the ventricular wall from a local electrode at the apex - similar to a wave initiated at the tip of an inverted cone before propagating up its walls. Two different pacing patterns were applied. The first used pacing bursts at a cycle length which was a fixed percentage of the tachycardia cycle length (determined by the size of the obstacles). This corresponds to "burst pacing" used in implantable cardiac defibrillators (ICD) [13]. The pacing cycle length as well as the number of extrastimuli in each pacing burst (4-8) were varied to look at their effects on the reentrant wave. The second was decremental ramp pacing in which the interval between successive extrastimuli was gradually reduced (corresponding to "ramp pacing" used in ICDs [13]).

Fig. 1: Pseudo-gray-scale plot of the e-field for the 2D Panfilov model (L = 256). The two square black patches are the non-conducting anatomical obstacles. The region of slow conduction is in the channel between the two non-conducting regions. The figure shows a "pacing" planar wave at the bottom of the simulation domain, propagating up towards the anatomical obstacles. The earlier pacing-stimulated wave is shown curving around the obstacles about to enter the narrow channel.

For a homogeneous cardiac medium, both ramp and burst pacing were unsuccessful at terminating reentry (see Discussion for mechanism). We also looked at the effect of anisotropy by making the conductivities along the vertical and the horizontal axes differ in a ratio of 1:0.3, which is consistent with cardiac tissue [14]. As with the homogeneous case, in the anisotropic case none of the pacing methods we tried were successful in terminating reentry.

However, we did achieve successful termination in the presence of inhomogeneity in the model. This was done by placing a small zone (= 7.5 mm) of slow conduction in the narrow channel between the two non-conducting patches. The conductivity in this region was 0.05 times smaller than the rest of the tissue. A 6-stimulus pacing burst was found to successfully block the anterograde branch of the extrastimulus traveling through the narrow channel - and hence terminate the reentry.

To understand the process of inhomogeneity-mediated termination we implemented a 1D model with a zone of slow conduction whose length and conductivity constant were varied to examine their effect on the propagation of the anterograde branch of the extrastimulus. The reentrant wave was started at a point in the ring (proximal to the zone of slow conduction) chosen to be the origin ($x = 0$) at time $t = T_0 = 0$. At time $t = T_1$, the first extrastimulus was given at $x = 0$ followed by a second extrastimulus at $t = T_2$ (Fig. 2). The first extrastimulus is able to terminate the reentry by itself if it is applied when the region to one end of it is still refractory -

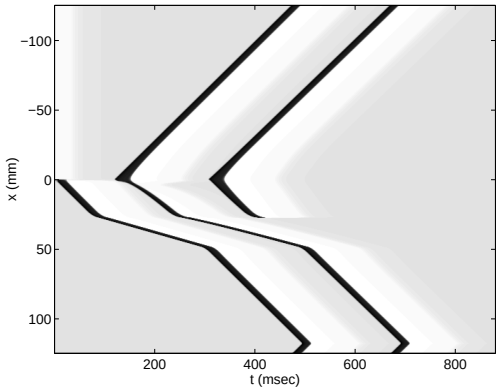

Fig. 2: Pseudograyscale plot of the e-field showing spatiotemporal propagation of reentrant wave in a 1D ring, successfully terminated by pacing with two extrastimuli. The zone of slow conduction is between x = 23 mm and x = 52 mm. In this region the conductivity constant changes from 1 to 0.1 unit with a gradient of 0.2 units/mm at the boundaries. The reentrant wave is initiated with a stimulus at x = 0 mm at T = 0 ms (with transient conduction block in the region $x < 0$). The first extrastimulus is applied at T_1 = 121 ms while the second is applied at T_2 = 308 ms (pacing site is $x = 0$ in both cases).

leading to unidirectional propagation. This is identical to the mechanism studied previously for terminating reentry in a 1D ring [6]. However, in this study we are interested in the effect of pacing from a site away from the reentry circuit. In that case, it is not possible for the first extrastimulus to arrive at the reentry circuit exactly at the refractory end of the reentrant wave (see the Discussion section). Therefore, we consider the case when the first extrastimulus is unable to block the anterograde conduction by itself. We have used values of T_1 for which the first extrastimulus can give rise to both the anterograde as well as the retrograde branches. Different values of coupling interval ($T_1 - T_0$) and pacing cycle ($T_2 - T_1$) were used to find which parameters led to block of the second anterograde wave.

IV. Discussion

Because the retrograde branch of the extrastimulus always mutually annihilates the reentrant wave, the success of pacing in terminating reentry around an anatomical obstacle depends on whether or not the anterograde branch of the extrastimulus is successfully blocked. Although apparently this is often achieved in practice (i.e., ICDs are often successful at antitachycardia pacing), as we have seen in our 2D model simulation, this is almost impossible to observe for homogeneous tissue unless the pacing site is located on the reentry circuit. Inhomogeneities appear to be necessary for termination, as outlined in the following simple mathematical argument.

Let us consider a reentrant circuit as a 1D ring of length L with separate entrance and exit sidebranches (Fig. 3). Further, let the pacing site be located on the entrance sidebranch at a distance z from the circuit. We use the entrance sidebranch as the point of spatial origin ($x = 0$) to define the location of the wave on the ring. The conduction velocity and refractory period at a location a distance x away (in the clockwise direction) from the origin is denoted by $c(x)$ and $r(x)$, respectively.

For a homogeneous medium, $c(x) = c$, $r(x) = r$ (c, r are constants). Therefore, the length of the region in the ring which is refractory at a given instant is $l = cr$. For sustained reentry

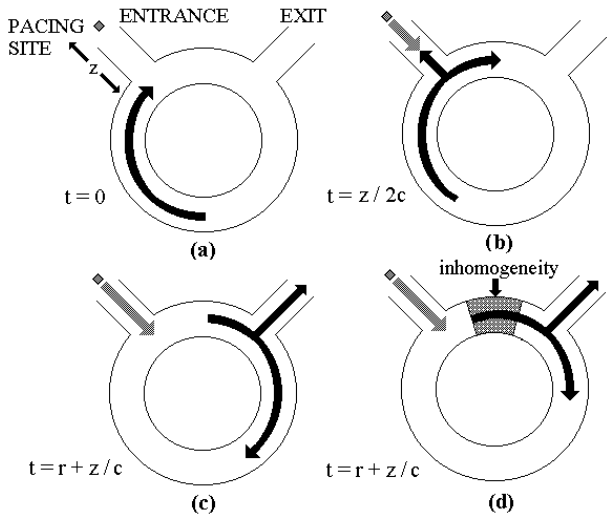

Fig. 3: Schematic diagram of reentry in a 1D ring illustrating the necessity of a region of inhomogeneity for successful termination of reentry by pacing. At $t = 0$ the reentrant wave reaches the entrance sidebranch (a). At $t = z/2c$ the reentrant wave propagating through the sidebranch and the first extrastimulus mutually annihilate each other (b). At $t = r + (z/c)$ the second extrastimulus reaches the reentry circuit by which time the refractory tail is a distance z away from the sidebranch (c). The presence of a region of inhomogeneity proximal to the pacing site makes it possible that the anterograde branch of the second extrastimulus will encounter a refractory region behind the reentrant wave (d).

to occur, there must be an area of excitable tissue between the front and the refractory tail of the reentrant wave - i.e., the excitable gap. The condition for existence of this is $L > c\,r$. For convenience, associate $t = 0$ with the time when the reentrant wave is at $x = 0$ (i.e., the entrance sidebranch) (Fig. 3(a)). Let us assume that an extrastimulus is given at $t = 0$. This extrastimulus will collide with the branch of the reentrant wave propagating out through the entrance sidebranch at $t = z/2c$ (Fig. 3(b)). The pacing site will recover at $t = r$ and if an extrastimulus is given again immediately it will reach the reentry circuit at $t = r + (z/c)$ (Fig. 3(c)). By this time the refractory tail of the reentrant wave will be at a distance $x = z$ away from the entrance sidebranch and the anterograde branch of the extrastimulus will not be blocked, i.e., it is impossible for the stimulus to catch up to the refractory tail in a homogeneous medium. This results in resetting of the reentrant wave rather than its termination. Note that if the first extrastimulus is given at a time $t < -z/c$, it reaches the reentry circuit before the arrival of the reentrant wave. As a result, the retrograde branch collides with the oncoming reentrant wave, while the anterograde branch proceeds to become the reset reentrant wave. It appears that only under the very special circumstance that the reentrant wave reaches the entrance sidebranch exactly at the same instant that the extrastimulus reaches the circuit, is there a possibility of the two waves colliding with each other leading to termination of reentry. However, if the circuit has any width, part of the reentrant wave is likely to survive and the wave will continue. Also such fine-tuning of pacing time is almost impossible in reality. As a result, pacing termination seems all but impossible if we consider the reentry circuit to be homogeneous.

The situation changes, however, if an inhomogeneity (e.g., a zone of slow conduction) exists in the circuit (Fig. 3(d)). In this case, the above argument no longer holds as the waves travel faster or slower depending on their location in the circuit. If the pacing site is proximal to the zone of slow conduction, then the pacing site may recover faster than points on the reentry circuit. As a result, extrastimuli may arrive at the circuit from the pacing site and encounter a region that is still recovering. This leads to successful block of the extrastimulus anterograde wave, while the retrograde wave annihilates the reentrant wave, resulting in successful termination. The success of pacing will depend on the location of the inhomogeneity. If pacing is performed distal to the zone of slow conduction, termination will be harder to achieve as the extrastimulus will have a longer distance to traverse before reaching the inhomogeneity, which will correspondingly have a longer time in which to recover. This is supported by electrophysiological studies of pacing in cardiac tissue [15].

Similar arguments may apply for other types of inhomogeneity. For example, existence of a region having longer refractory period than normal tissue will lead to the development of patches of refractory zones in the wake of the reentrant wave. If the anterograde branch of the extrastimulus arrives at such a zone before it has fully recovered, it will be blocked. In fact, a computer modeling study of the interruption of tachycardia through pacing has been performed assuming the existence of such a region on the reentrant circuit [4].

By providing simulation results of 1D and 2D models in which pacing is unsuccessful in terminating anatomical reentry in the absence of any inhomogeneities and providing a simple mathematical argument in support of this conclusion, this paper outlines the potential significance of inhomogeneities in cardiac tissue in the termination of VT through pacing.

V. Conclusion

There are obvious limitations of our study - the most prominent being the use of excitable media models of ventricular activity. These models do not incorporate details of ionic currents (unlike, e.g., the Luo-Rudy model) but rather lump such details into a single model parameter. Further, we have used 1D or 2D models in our study, even though the heart's 3D structure is important in reentry. We have also assumed the heart to be a monodomain rather than a bidomain (which has separate equations for intracellular and extracellular space) - for the low antitachycardia pacing stimulus amplitude we believe this simplification to be justified.

Despite these limitations, the results presented here may apply to the case of pacing termination of anatomical reentry in the ventricle. We have tried to develop general (i.e., model-independent) mathematical arguments about the requirement that inhomogeneities should exist in the reentrant circuit for pacing to be successful in eliminating VT.

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